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WASHINGTON, DC 20460

Mary B.
CPR

MAY 8 1997

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Diuron

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Health Effects Division (7509C)
and
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THROUGH: Stephanie R. Irene, Ph.D.
Deputy Director, Health Effects Division (7509C)

TO: Philip Errico
Product Manager #25
Fungicide-Herbicide Branch
Registration Division (7505C)
and
Larry Schnaubelt
Special Review and Reregistration Division (7508W)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on December 18, 1996 to discuss and evaluate the weight-of-the-evidence on Diuron with particular reference to its carcinogenic potential. In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 23, 1996) Diuron was characterized as a "known/likely" human carcinogen by all routes, based on urinary bladder carcinomas in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. Information from structurally related analogs provided further support.

The CPRC recommended that for the purpose of risk characterization, a low dose linear extrapolation model be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the male rat.

①

SUMMARY

Administration of Diuron in the diet to NMRI mice resulted in increases in mammary gland adenocarcinomas in female mice which had statistically significant positive trends; there were no pairwise statistically significant increases. The incidence of tumors at the highest dose (2500 ppm) exceeded that in historical controls from the testing facility. There were no apparent significant increases in tumors in male mice. The CPRC agreed that dosing in the mouse was adequate, and not excessive.

Administration of Diuron in the diet to Wistar rats resulted in statistically significant increases in urinary bladder carcinomas at the highest dose (2500 ppm) in both sexes; there were also statistically significant positive trends in both sexes. The incidences at the highest dose was 73% and 27% (vs 2% in concurrent controls) in males and females, respectively and were well in excess of historical controls from the testing facility. In male rats at the highest dose, there were also increases in renal epithelial carcinomas and combined papilloma/carcinoma which had a statistically significant trend for the combined tumors only. There were no pairwise statistically significant increases in kidney tumors; however the numerical increase in carcinomas alone (4% vs 0% in concurrent controls) was considered to be biologically significant because of the rarity of this tumor type. In addition, hyperplasia of the urinary bladder at lower doses noted in both the rat and mouse studies provided further support that the kidney tumors (as well as the bladder tumors) were compound-related. The CPRC agreed that dosing in the rat was adequate, and not excessive.

There were no data provided by the Registrant to attribute a mechanism for the carcinogenic response in mice or rats.

Diuron is structurally related to Linuron, Fluometuron and Monuron which all have demonstrated carcinogenic activity at various sites in rodents. Only Monuron is associated with tumors in the kidney; however, differences in metabolism may account for the site differences of the other analogs. Diuron was only weakly positive (considered to be equivocal) in an in vivo cytogenetic study; other submitted mutagenicity studies were negative or inadequate. Information from structurally related analogs provided further support.

A. **Individuals in Attendance at the meeting:**

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William Burnam

William Burnam

Marion Copley

Marion Copley

Kerry Dearfield

Kerry Dearfield

Elizabeth Doyle

Elizabeth Doyle

Yiannakis Ioannou

Yiannakis Ioannou

Esther Rinde

Esther Rinde

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Linda Taylor¹

Linda Taylor

Clark Swentzel

Clark Swentzel

Lori Brunsman

Lori Brunsman

Lucas Brennecke²
(PAI/ORNL)

See 3a

3. Other Attendees: Albin Kocialski and Bernice Fisher (HED)

¹Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

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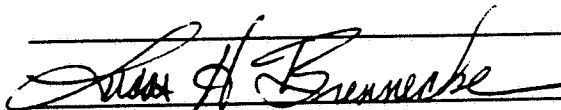
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3. Other Attendees: Albin Kocialski and Bernice Fisher
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B. Material Reviewed

The material available for review consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. Taylor, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information

DIURON, 3-[3,4-dichlorophenyl]-1,1-dimethylurea is a substituted urea herbicide effective against emerging and young broadleaf and grass weeds and mosses. Tolerances for residues in or on asparagus, Bermuda grass, Bermuda grass hay; alfalfa, corn fodder or forage [sweet corn field corn, popcorn], grass crops [other than Bermuda], grass hay [other than Bermuda], hay, forage and straw of barley, oats, rye, and wheat, hay and forage of birdsfoot trefoil, clover, peas, and vetch, peppermint hay, sorghum fodder and forage; apples, artichokes, barley grain, blackberries, blueberries, boysenberries, citrus fruits, corn in grain and ear form [including sweet, field and popcorn], cottonseed, currants, dewberries, gooseberries, grapes, huckleberries, loganberries, oat grain, olives, pears, peas, pineapple, potatoes, raspberries, rye grain, sorghum grain, sugarcane, vetch (seed), wheat grain; meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep; bananas, nuts, and peaches; and papayas have been established. The CAS Registry Number [CAS NO.] is 150-68-5. The PC Code is 035505. The Tox. Chemical No. is 410.

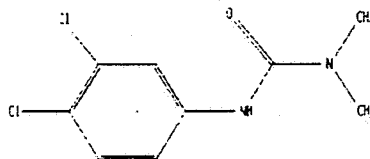


Figure 2 Diuron

D. Evaluation of Carcinogenicity Evidence

1. Carcinogenicity Study in Mice

Reference: DIURON: Study for Chronic Toxicity and Carcinogenicity with NMRI Mice (Administration in Diet for 24 Months). [Study # Bayer AG T 4010922, DuPont Report # DIUR/TOX9, dated October, 1983 [translation completed January, 1991]; MRID # 42159501; Document Nos. 009486 and 010902011030. Addendum: MRID # 43349301 [Supplemental Data and Background Tumor Incidences].

a. Experimental Design

Groups of Bor strain NMRI [SPF HAN] mice of both sexes [50 mice/sex/dose (carcinogenicity); 10 mice/sex/group (12-month interim group)] were administered Diuron [98.7% pure] via the diet at dose levels of 0, 25 ppm [♂♂ 5.5/♀♀ 7.5 mg/kg/day], 250 ppm [♂♂ 50.8/♀♀ 77.5 mg/kg/day], or 2500 ppm [♂♂ 640.1/♀♀ 869.0 mg/kg/day] for 24 months.

b. Discussion of Tumor Data

MALES - There were no statistically-significant tumors observed in male mice.

FEMALES - Female mice had significant increasing trends in mammary gland adenocarcinomas and ovarian luteomas, both at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls. [Table 8 from L. Brunzman memo dated 11/20/96; reproduced here as Table 1].

TABLE 1. DIURON - NMRI Mouse Study

Female Mammary Gland and Ovarian Tumor Rates⁺ and Peto's Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
	0	25	250	2500
Mammary Gland Adenocarcinomas (%)	2/34 (6)	1 ^a /29 (3)	1/44 (2)	6/37 (16)
p =	0.016 [*]	0.560	0.403	0.159
Ovarian Luteomas (%)	3/34 (9)	1/32 (3)	2/46 (4)	7 ^b /41 (17)
p =	0.024 [*]	0.330 ⁿ	0.358 ⁿ	0.243

⁺Number of tumor bearing mice/Number of mice examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice mice.

^aFirst mammary gland adenocarcinoma observed at week 78, dose 25 ppm.

^bFirst uterine luteoma observed at week 53, dose 0 ppm, in an interim sacrifice mouse. Second uterine luteoma observed at week 72, dose 2500 ppm, in a mouse that died on study.

ⁿNegative change from control.

() Percent

Note: One animal in the control group of the interim sacrifice group had a uterine luteoma. Interim sacrifice mice are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If , then $p < 0.05$. If , then $p < 0.01$.

FEMALES: When compared to historical control data from published papers of studies on NMRI mice, the Registrant stated that spontaneous ovarian tumors are usually rare in mice except in certain strains, which include Han:NMRI mice. From the literature, the incidence of ovarian tumors in these mice can be influenced by the age at terminal sacrifice, husbandry conditions, source of stock, and the nutritional status [i.e., obese vs lean], and variability among pathologists in classification of these tumors affects the reported incidence. The Registrant stated that primary ovarian tumors are classified on the assumption that these tumors arise from one of three ovarian components: epithelium [either of the ovarian surface or rete ovarii], germ cells, or ovarian stroma, including sex cords, which probably contribute cells to ovarian follicles and thus to the endocrine apparatus of the ovary. Tumors of the latter group are termed sex cord-stromal tumors and include granulosa cell tumors, luteomas, thecomas, Sertoli cell tumors of the ovary, Leydig cell tumors, androblastoma, arrhenoblastoma, or lipid cell tumors. It is further stated that NTP recommends combining the incidence of the sex cord-stromal tumors for statistical assessment of tumor data. In addition to the similarity in the histogenesis of the granulosa/theca cell tumors and luteomas, any one of these tumors may have components of the other. For this reason, several groups of pathologists consider luteoma and thecoma as morphologic variants of granulosa cell tumors, differing only in their degree and direction of differentiation. Therefore, the Registrant combined the sex cord-stromal tumors [Table 2] in the ovaries and analyzed by the Cochran-Armitage test for trend and found no significant increase in tumors and the percent incidence falls within the reported range for spontaneous occurrence [0-35.5%]. Also provided were historical control data from 18 studies performed at the BAYER testing facility. With respect to ovarian tumor data, 9 of the 18 studies list luteoma [0-6.8%], and the highest number is 3, which occurred in 2 studies [3/44 and 3/45 mice].

Table 2. Ovarian Tumor Incidence - Registrant's Analysis				
Tumor/Dose	0 ppm	25 ppm	250 ppm	2500 ppm
OVARIAN TUMORS n=	50	47	49	50
<u>granulosa/thec. tumors unilat.</u>				
benign	7 [14]♦	4 [9]	11 [22]	5 [10]
bilat. benign	1 [2]	1 [2]	2 [4]	2 [4]
unilat. malignant	0	1 [2]	0	0
<u>luteoma</u>				
unilat. benign	3 [6]	0	2 [4]	7 [14]**
bilat. benign	0	1 [2]	0	0
<u>combined sex cord-stromal tumors‡</u>	11 [22]	7 [15]	15 [31]	14 [28]
<u>tubular cystadenoma, benign</u>	2 [4]	1 [2]	1 [2]	0
<u>leiomyoma, unilat. benign</u>	0	0	0	1 [2]
<u>teratoma, unilat. benign</u>	0	1 [2]	0	0

♦ (%); ‡ sum of all sex cord-stromal tumors, including all granulosa/theca tumors and all luteomas; ** p<0.01

At the Diuron Carcinogenicity Peer Review meeting December 18, 1996, it was decided that the female mouse ovarian tumor rates table should reflect the more appropriate "combined sex chord-stromal tumors" nomenclature in lieu of the "luteoma" terminology used in the qualitative risk assessment (Lori L. Brunzman to Linda L. Taylor, 11/20/96). Dr. Lucas Brennecke, EPA's consulting pathologist, confirmed that the combined tumor counts are more appropriate than the individual counts for ovarian tumors, as it is difficult to distinguish between the different types of ovarian tumors. Since only the luteoma tumor counts have been verified, the counts for the combined sex chord-stromal tumors have been taken from Table 2, page 3, of the Diuron data package, which was extracted from the registrant's analysis.

Female mice do not have a significant increasing trend, or any significant differences in the pair-wise comparisons of the dosed groups with the controls, for ovarian combined sex cord-stromal tumors [L. Brunzman memo dated 12/18/96]. This statistical analysis was based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Table 1a for female mouse ovarian tumor analysis results.

Table 1a. Diuron - NMRI (SPF HAN) Mouse Study
Female Ovarian Tumor Rates⁺ and Exact Trend Test
and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	25	250	2500
Combined Sex Cord- Stromal Tumors (%)	11/34 (32)	7/32 (22)	15/46 (33)	14/41 (34)
p =	0.268	0.249 ⁿ	0.588	0.534

⁺Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice animals.

ⁿNegative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If , then p < 0.05. If , then p < 0.01.

With regard to the mammary gland, the Registrant states that mouse mammary gland tumors are classified as 1) adenocarcinoma type A [synonyms: adenoma simple, acinar carcinoma, adenocarcinoma simple], 2) adenocarcinoma type B [synonyms: irregular tubular adenocarcinoma, solid polygonal-cell carcinoma, intratubular carcinoma, papillary cystic adenocarcinoma, intracanalicular adenocarcinoma], 3) adenocarcinoma type C [synonyms: fibroadenoma, adenofibroma], 4) adenocanthoma [synonyms: keratinizing tumors, mammary tumor with keratinization, squamous carcinoma, metaplastic carcinoma, adenocarcinoma, variable, type IV], 5) carcinosarcoma [synonyms: spindle-cell carcinoma, sarcomatoid carcinoma], 6) sarcoma, and 7) miscellaneous tumors. It is stated that the mammary tumors observed in the Diuron study in mice are synonymous with adenocarcinoma types A and B. Their analysis shows a statistically significant increase in the incidence of malignant [12%] mammary adenocarcinomas in the high-dose females. The spontaneous incidence of malignant mammary gland tumors [carcinoma, Types A/B combined] in Han:NMRI female mice is stated to be 9-14% in ad libitum fed mice and 2-9% in food restricted fed mice. There is no age-specific appearance of carcinomas. The Registrant concludes that because the incidence is within the published historical control range, Diuron is not carcinogenic for the mammary gland [Table 3]. In the historical control data from the testing facility [16 studies], the highest number of mice observed with a malignant mammary gland tumor was 3, which occurred in 3 studies [3/48, 3/48, 3/49 mice; range 0-6.3%].

Table 3. Mammary Tumor Incidence - Registrant's Analysis				
Tumor/Dose [ppm]	0	25	250	2500
MAMMARY GLAND TUMORS n=	50	47	49	50
mammary adenocarcinoma,	2	1	1	6*
malignant	[4]	[2]	[2]	[12]
mammary carcinoma,	♦	1	0	0
anaplastic, malignant	0	[2]	1	6*
mammary gland tumors,	2	2	[2]	[12]
combined	[4]	[4]		

♦ [%]; * p<0.05

c. Non-Neoplastic Lesions

MALES: The incidence of several non-neoplastic liver lesions was significantly increased at the high dose compared to the concurrent control [Table 4]. There were no adverse findings in the urinary bladder.

Tissue/Lesion/ Dose (ppm) MALES	Table 4. Microscopic Findings - Non-Neoplastic [n/n]			
	0	25	250	2500
Liver N=	45/46	48/38	46/48	46/46
enlarged degenerative	0/0	0/1	0/3	0/10**
hepatopathy	1/0	0/0	0/0	15**/0
increased mitosis	1/0	2/3	0/0	8**/4*
single cell necrosis	3/12	2/7	5/10	7*/19**
↑ accumulation of Kupffer Cells	6/9	6/9	8/9	11*/9

* p<0.05; ** p<0.01;

FEMALES: The incidence of non-neoplastic lesions in the mammary gland and ovaries were comparable among the groups. At the high-dose level, there was an increased incidence of epithelial hyperplasia, edema, and thickened mucosa in the urinary bladder [Table 5]. Liver lesions were also increased at the high-dose level [Table 4].

Tissue/Lesion/ Dose (ppm) FEMALES	Table 5. Microscopic Findings - Non-Neoplastic			
	0	25	250	2500
Urinary Bladder N=	46	36	45	44
epithelial hyperplasia	5	5	3	23**
edema	0	0	0	17**
mucosa thickened	0	0	0	5**

* p<0.05; ** p<0.01; data from page 62 of report.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The statistical evaluation of mortality indicated no significant incremental change with increasing doses of Diuron in either male or female mice. The highest dose tested [2500 ppm] was considered adequate. Signs of toxicity at this dose level include (1) decreased body weight gain for both sexes [♂♂ 90%/♀♀ 87% of control overall], (2) increased spleen and liver weights in males, (3) increased leucocyte and reticulocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, and bilirubin values in both sexes, (4) increased incidence of intracellular pigments in the renal tubules in females and in the spleen of both sexes, (5) increased incidence of hemosiderin deposits in liver cells in males, (6) increased incidence of liver single cell necrosis and cell mitosis in both sexes, (7) increased incidence of enlarged degenerative cells in the liver in females and of hepatopathy and accumulation of Kupffer cells in males, and (8) increased incidence of urinary bladder edema and epithelial hyperplasia, thickened mucosa, and enlarged uterine horn in females. The HED RfD Committee discussed Diuron at the 9/26/96 meeting and concluded that the study was acceptable; i.e., the dose levels were considered adequate. **The NOEL is 250 ppm [♂♂ 50.5/♀♀ 77.5 mg/kg/day], and the LOEL is 2500 ppm [♂♂ 640.1/♀♀ 869.0 mg/kg/day],** based on the effects listed above. The CPRC agreed that dosing in the mouse study was adequate (not excessive) for assessing the carcinogenicity potential of Diuron in mice.

2. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Diuron: Study for Chronic Toxicity and Carcinogenicity with Wistar Rats (Administration in Diet for up to Two Years) [BAYER AG T 8010647; DuPont Report No. D/Tox 17, dated 11/29/85; MRID # 40886501; Document No. 008160].

a. Experimental Design

Wistar rats [50/sex/group for 104 weeks; 10/sex/group for interim 52-week sacrifice] were fed Diuron at dose levels of 0, 25 ppm [♂♂ 1.02/♀♀ 1.69 mg/kg/day], 250 ppm [♂♂ 10.46/♀♀ 16.88 mg/kg/day], or 2500 ppm [♂♂ 111.17/♀♀ 202.22 mg/kg/day].

b. Discussion of Tumor Data

MALES: Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined, all at p

< 0.01. Male rats also had a significant increasing trend in kidney renal pelvis epithelial papillomas and/or carcinomas combined at $p < 0.05$. [Tables 3 and 4 of L. Brunsmann memo, reproduced here as Tables 6 and 7].

FEMALES: Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined, all at $p < 0.01$. [Table 5 of L. Brunsmann memo, reproduced here as Table 8].

Table 6. DIURON - Wistar Rat Study

Male Urinary Bladder Epithelial Tumor Rates* and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	25	250	2500
Papillomas (%)	0/49 (0)	0/50 (0)	0/49 (0)	1 ^a /48 (2)
p =	0.245	1.000	1.000	0.495
Carcinomas (%)	1/49 (2)	0/50 (0)	1/49 (2)	35 ^b /48 (73)
p =	0.000 ^{**}	0.495 ⁿ	0.753	0.000 ^{**}
Combined (%)	1/49 (2)	0/50 (0)	1/49 (2)	35 ^c /48 (73)
p =	0.000 ^{**}	0.495 ⁿ	0.753	0.000 ^{**}

*Number of tumor bearing rats/Number of rats examined, excluding those that died or were sacrificed before week 53. Also excludes week 52 interim sacrifice animals.

^aFirst papilloma observed at week 104, dose 2500 ppm.

^bFirst carcinoma observed at week 81, dose 2500 ppm.

^cOne rat in the 2500 ppm dose group had both a papilloma and a carcinoma.

ⁿNegative change from control.

()Percent

Note: Interim sacrifice rats are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If , then $p < 0.05$. If , then $p < 0.01$.

Table 7. DIURON - Wistar Rat Study

Male Kidney Renal Epithelial Tumor Rates* and Exact
Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	25	250	2500
Papillomas	0/49	0/50	0/50	1 ^a /48
(%)	(0)	(0)	(0)	(2)
p =	0.244	1.000	1.000	0.495
Carcinomas	0/49	0/50	0/50	2 ^b /48
(%)	(0)	(0)	(0)	(4)
p =	0.058	1.000	1.000	0.242
Combined	0/49	0/50	0/50	3/48
(%)	(0)	(0)	(0)	(6)
p =	0.014*	1.000	1.000	0.117

*Number of tumor bearing rats/Number of rats examined, excluding those that died or were sacrificed before week 53. Also excludes week 52 interim sacrifice rats.

^aFirst papilloma observed at week 104, dose 2500 ppm.

^bFirst carcinoma observed at week 104, dose 2500 ppm.

Note: Interim sacrifice rats are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If , then $p < 0.05$. If , then $p < 0.01$.

Table 8. DIURON - Wistar Rat Study

Female Urinary Bladder Epithelial Tumor Rates* and Exact
Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	25	250	2500
Papillomas (%)	0/47 (0)	0/49 (0)	2 ^a /50 (4)	0/49 (0)
p =	0.560	1.000	0.263	1.000
Carcinomas (%)	1/47 (2)	0/49 (0)	1/50 (2)	13 ^b /49 (27)
p =	0.000 ^{**}	0.490 ⁿ	0.737	0.001 ^{**}
Combined (%)	1/47 (2)	0/49 (0)	3/50 (6)	13 ^c /49 (27)
p =	0.000 ^{**}	0.490 ⁿ	0.332	0.001 ^{**}

*Number of tumor bearing rats/Number of rats examined, excluding those that died before week 44. Also excludes week 52 interim sacrifice rats.

^aFirst papilloma observed at week 104, dose 250 ppm.

^bFirst carcinoma observed at week 44, dose 2500 ppm.

^cOne rat in the 2500 ppm dose group had both a papilloma and a carcinoma.

ⁿNegative change from control.

Note: Interim sacrifice rats are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If , then $p < 0.05$. If , then $p < 0.01$.

When compared to historical controls of the testing facility, the incidence of transitional epithelial carcinomas [malignant tumors of the bladder epithelium] at the high-dose level exceeds the historical control incidence [range not provided], and the maximum [2%] incidence at the low- and mid-dose levels was said to be within the spontaneous rate. With regard to the uterus, the slight increase in the number of adenocarcinomas and total malignant neoplasias observed at the high-dose level was not statistically significant either on a pairwise comparison or trend basis [personnel communication from L. Brunsman]. The spontaneous incidence of adenocarcinomas was listed as 2%-20%, with a mean of 8%.

Table 9. Uterine Tumor Incidence				
Tumor/Dose [ppm]	0	25	250	2500
UTERUS n=	48	50	50	50
adenocarcinoma, malignant	5	5	5	9
endometrial sarcoma, malignant	0	0	0	2
squamous cell carcinoma, malignant	0	0	1	1

c. Non-Neoplastic Lesions

MALES There was an increased incidence of hyperplasia in the renal pelvis and urinary bladder with dose, and the severity of the lesion was also increased [Table 10]. In the kidney, round cell infiltration was increased at the high-dose level compared to the control and lower dose levels.

Table 10. Non-neoplastic Lesions in the Male Rat				
Lesion/Dose	0 ppm	25 ppm	250 ppm	2500 ppm
Renal Pelvis				
# examined	50	50	50	47
focal hyperplasia/epithelium total	37	37	45	43
Grade 1	31	30	18	3
Grade 2	5	7	25	23
Grade 3	1	0	2	17
Urinary Bladder				
# examined	50	50	50	49
urothelial hyperplasia total	13	5	16	14
Grade 1	11	5	15	1
Grade 2	2	0	1	3
Grade 3	0	0	0	10
Kidney				
# examined	50	50	50	49
round cell infiltration	3	12	9	31
Spleen				
# examined	50	50	50	49
hyperemia/blood congestion	0	0	1	15
fibrosis	0	0	3	16
Thyroids				
# examined	50	48	50	49
C cell hyperplasia	29	27	37	39
Bone Marrow				
# examined	50	50	50	49
activated	0	5	7	42

FEMALES There was an increased incidence of hyperplasia in the renal pelvis and urinary bladder with dose, and the severity of the lesion was also increased [Table 11]. Glandular-cystic hyperplasia was increased slightly at the high-dose level, and the high-dose displayed increased fibrosis in the spleen. Increased incidences of lesions also occurred in the liver, thyroid, and bone marrow.

Table 11. Non-neoplastic Lesions in the Female Rat				
Lesion/Dose	0 ppm	25 ppm	250 ppm	2500 ppm
Renal Pelvis				
# examined	48	50	50	47
focal hyperplasia/epithelium total	23	25	46	42
Grade 1	20	22	12	5
Grade 2	3	3	30	33
Grade 3	0	0	4	4
Urinary Bladder				
# examined	48	49	50	50
urothelial hyperplasia total	11	7	17	30
Grade 1	10	7	9	4
Grade 2	1	0	3	17
Grade 3	0	0	5	9
Kidney				
# examined	48	49	50	50
round cell infiltration	7	9	12	3
Uterus				
# examined	48	50	50	50
glandular-cystic hyperplasia	3	5	2	7
Spleen				
# examined	48	50	50	50
hemosiderin storage	44	46	50	49
fibrosis	0	0	0	17
Liver				
# examined	48	50	50	50
fatty degeneration	0	0	1	3
round cell infiltration	4	9	10	13
hyperemia	19	32	33	36
bile duct infiltration	16	10	15	25
vacuolar degeneration of liver cells	0	1	3	11
Thyroids				
# examined	47	49	50	48
C cell hyperplasia	17	23	30	28
Bone Marrow				
# examined	48	50	50	50
activated	5	12	22	42

d. Adequacy of Dosing for Assessment of Carcinogenicity

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Diuron in either male or female rats. The HED RfD Committee discussed Diuron at the 9/26/96 meeting and concluded that the rat study was Acceptable as supplementary data due to deficiencies with respect to the examination of organs. Specific concern was expressed that the mammary gland was not examined in the rat study, given the fact that mammary gland tumors were observed to be increased in the mouse study. There was no NOEL determined in the rat study, and the LOEL was considered to be 25 ppm, the lowest dose tested, based on decreased erythrocyte count in

females, increased hemosiderin in the spleen, increased spleen weight, bone marrow activation, increased hematopoietic marrow, decreased fat marrow, and thickened urinary bladder wall in males. The RfD Committee recommended that the chronic toxicity/carcinogenicity study in rats be repeated. The CPSC concluded that the dosing in the rat study was adequate (not excessive) for assessing the carcinogenic potential of Diuron in rats.

E. Additional Toxicology Data on Diuron

1. Metabolism

Reference: Although the HED Metabolism Peer Review Committee expressed concern about the lack of metabolism data for Diuron in the rat, and TB II informed SRRD that the Registrant should be requested to submit a rat metabolism study [memo dated 11/18/93], no study was located in the files.

2. Mutagenicity

References: (a) Rickard, L.B., et al. [1985]. Mutagenicity Evaluation of Diuron in the CHO/HGPRT Assay MRID# 00146609; Document No. 005039] (b) Sarraf, A. [1985]. Assessment of Diuron in the In Vivo Cytogenetic Study in Rats MRID# 00146611, Document No. 005039] (c) Arce, G.T. and Sarraf, A.M. [1985]. Assessment of Diuron in the In Vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes MRID# 00146610; Document No. 005039] (d) Arce, G.T. [1987] Mutagenicity Evaluation (of Diuron) in Salmonella typhimurium MRID#s 00146608 and 40228805; Document Nos. 005039 and 008751].

a. CHO/HGPRT assay. Negative. Under the conditions of the experiment, Diuron up to cytotoxic levels with and without metabolic activation was negative.

b. In vivo cytogenetic study in rats. Positive Under the conditions of the assay, Diuron was weakly clastogenic at 5000 mg/kg, the highest dose tested [HDT].

c. In vitro unscheduled DNA synthesis [UDS] assay. Negative. Under the conditions of the assay, doses of Diuron up to 20 mM [HDT] were negative, but the RfD Committee recommended reevaluation of the study.

d. Salmonella typhimurium reverse gene mutation assay. Negative. Under the conditions of the study, the results were negative.

3. Structure-Activity Relationship

Diuron is a substituted urea herbicide. (1) **Linuron** is classified a Group C carcinogen without quantitation [hepatocellular adenomas in female CD-1 mice at HDT [1500 ppm] and testicular adenoma/hyperplasia in male Crl:CD(SD)BR Sprague-Dawley rats. Linuron was negative in the Ames assay at dose levels up to 5 g/plate, with and without activation; did not produce gene mutations in an *in vitro* assay using CHO cells both with and without activation; did not induce bone marrow chromosome aberrations *in vivo*; did not induce unscheduled DNA synthesis in rat hepatocytes. (2) **Fluometuron** classified a Group C carcinogen with both a low-dose extrapolation model (Q^*_1) applied to the animal data [lung tumors in male CD-1 mice] and the Reference Dose [RfD] approach [combined adenomas/carcinomas of the lungs in male mice and malignant lymphocytic lymphomas in female mice [dose levels considered inadequate-too low]. Fluometuron did not induce UDS in primary rat hepatocytes at dose levels that were sufficiently high; was negative for inducing micronuclei at a toxic dose level; and was negative in the Ames assay when tested up to the limit dose [5000 μ g/plate]. (3) **Monuron** has not been reviewed by HED CPRC. Kidney and liver tumors have been reported in F344/N rats; malignant gastric adenoma, microcellular cancer of lung, seminoma in testes in rats and benign hepatoma, alveolocellular cancer and cancer of the kidney have been reported in old Russian studies. (4) **Siduron** was not reviewed by CPRC and data has not been reviewed. During the Phase II review, mutagenicity studies were identified and assessed as adequate for review, and a 2-year rat study was to be submitted; there is no evidence that the studies were forwarded to HED for review.

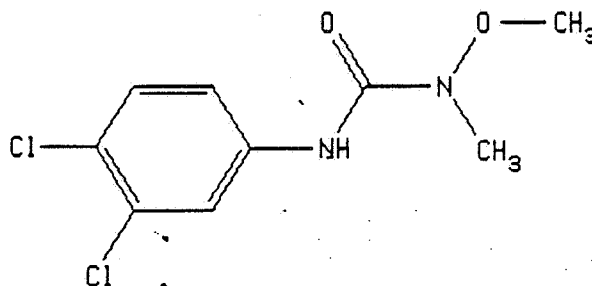


Figure 3 Linuron

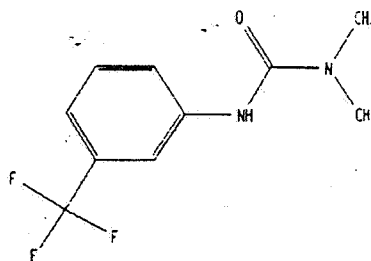


Figure 4 Fluometuron

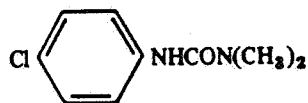


Figure 5 Monuron

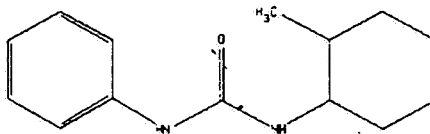


Figure 6 Siduron

F. Weight of Evidence Considerations

The Committee was asked to consider the following facts regarding the toxicology data on Diuron in the Weight-of-the-Evidence determination of its carcinogenic potential:

1. Male and female NMRI (SPF Han) mice were fed 0, 25, 250, or 2500 ppm of Diuron for 104 weeks. There was no adverse effect on survival of either sex. Neoplastic findings were observed only at the high dose in females compared with the controls.

Female mice had a significant increasing trend in mammary gland adenocarcinomas at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The incidence of this tumor appears to be outside the testing facility's historical control.

2. Wistar rats were fed Diuron at dose levels of 0, 25 ppm [$\delta\delta$ 1.02/ $\eta\eta$ 1.69 mg/kg/day], 250 ppm [$\delta\delta$ 10.46/ $\eta\eta$ 16.88 mg/kg/day], or 2500 ppm [$\delta\delta$ 111.17/ $\eta\eta$ 202.22 mg/kg/day]. There was no adverse effect on survival of either sex. Neoplastic findings were observed in the urinary bladder of both sexes and in the renal pelvis of the males compared with the controls.

Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined. Male rats also had a significant increasing trend in kidney renal pelvis epithelial papillomas and/or carcinomas combined.

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined.

The incidence of these tumors is greater than the historical control incidence.

3. From the submitted studies, Diuron was very weakly positive in the rat in vivo cytogenetic assay at 5000 mg/kg, negative in the CHO/HGPRT assay, negative in the in vitro UDS assay and negative in the reverse gene mutation assay in Salmonella typhimurium. There is little identified mutagenic concern with respect to Diuron.

4. Structure-Activity. Linuron is a Group C carcinogen without quantitation [hepatocellular adenomas in female CD-1 mice at HDT [1500 ppm] and testicular adenoma/hyperplasia in male Crl:CD(SD)BR Sprague-Dawley rats. Fluometuron is a Group C carcinogen with both a low-dose extrapolation model (Q_1^*) applied to the animal data [lung tumors in male CD-1 mice] and the Reference Dose [RfD] approach [combined adenomas/carcinomas of the lungs in male mice and malignant lymphocytic lymphomas in female mice [dose levels considered inadequate-too low].

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the *EPA proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996) for classifying the weight of evidence for Diuron.

In accordance with these proposed Guidelines, the CPRC unanimously agreed to characterize the weight of the evidence for Diuron as "known/likely" to be carcinogenic to humans by all routes of exposure based on: the robust tumor response of carcinomas in the urinary bladder in both sexes of the Wistar rat; kidney carcinomas (a rare tumor) in the male Wistar rat; and mammary gland carcinomas in the female NMRI mouse. There is no known data on human exposure to Diuron.

Diuron is a member of a chemical class (substituted ureas) of which Linuron, Fluometuron and Monuron have demonstrated carcinogenic activity at various sites in rodents. Diuron was only weakly positive in an in vivo cytogenicity study, which was considered to be equivocal and other submitted mutagenicity studies were either negative or inadequate.

No mechanistic or mode of action data were presented to justify the quantification of human risk by a method other than the low-dose linear extrapolation default. The CPRC recommended that for the purpose of risk characterization, a low dose linear extrapolation model be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the male rat.

The CPRC recommended that the in vivo cytogenicity study be repeated.